benzisoxazolylamino, purinylamino, quinazolinylamino, quinolizinylamino, quinolinylamino, isoquinolinylamino, quinoxalinylamino, naphthyridinylamino, pteridinylamino, carbazolylamino, azepinylamino, diazepinylamino, acridinylamino, pyrazolinylamino, indolinylamino, pyrrolidinylamino, piperidinylamino, piperazinylamino, diazepinylamino, morpholinylamino, thiomorpholinylamino, oxazolidinylamino, oxazolinylamino, oxazepinylamino, aziridinylamino and tetrahydrofuranylamino.

REMARKS

Reconsideration and withdrawal of the rejections of and objections to the claims are respectfully requested in view of the amendments and remarks which follow.

Claims 1, 2, 5-32, 34-37, 46, 48, and 64-67 have been canceled. New claims 68-101 have been added to ore distinctly claim that which Applicants regard as their invention. New claims 68 and 69 correspond to prior claims 1 and 2; new claims 70-71 correspond to prior claims 5-6; new claims 72-82 correspond to prior claims 9-19; new claim 83 corresponds to prior claim 21; new claim 84 corresponds to prior claim 23; new claims 85-92 corresponds to prior claims 25-32; new claims 93-96 correspond to prior claims 34-37; new claim 97 corresponds to prior claim 46; new claim 98 corresponds to prior claim 48 and new claims 99-101 correspond to prior claims 65-67. Support for the new claims can be found in the specification and claims as originally filed. No new matter is added by this amendment.

I. The Rejection of the claims under 35 U.S.C. § 112, first paragraph

A. Enablement

Claims 1-3, 5-44, 46, and 48 were rejected under 35 U.S.C. § 112, first paragraph, because: (a) the claims are still not commensurate in scope as to the diversity of Markush groups, aromatic groups, heteroaromatic and heterocyclic groups which all permit further substitution on the purine ring; (b) the scope of a functional group which can be converted to hydrogen *in vivo* is allegedly not adequately enabled by the specification and (c) in claims 46 and 48, the instant claim language embraces disorders not only for treatment but also for prevention.

1. The claims are still not commensurate in scope as to the diversity of Markush groups, aromatic groups, heteroaromatic and heterocyclic groups which all permit further substitution on the purine ring

This rejections are respectfully traversed. However, in order to advance prosecution, Applicants have canceled claim 1; new claim 68 recites specific embodiments. Applicants reserve the right to file subsequent continuation and/or divisional applications on canceled subject matter.

It is respectfully asserted that the specification fully enables one skilled in the art to practice the full scope of the claimed invention. The specification fully describes the various types of functional groups that can be used for the various X, Y, A, Z and R's in the different positions of the compounds of formula I. The specification defines these functional groups, including representative example for each of these groups, on pages 4 through 9. For example, the term C_{1-6}-alkyl is defined as a branched or straight hydrocarbon group having from 1 to 6 carbon atoms, and includes a discussion of typical C_{1-6}-alkyl groups as including, but not limited to, methyl, ethyl, n-propyl, isopropyl, butyl, isobutyl, *sec*-butyl, *tert*-butyl, pentyl, isopentyl, hexyl, isohexyl, and the like. (Specification, page 4) No special definitions are included in the specification and all terms are defined in such a way that they have their conventional meaning as used by one of ordinary skill in the chemical arts.

Further, the specification includes numerous synthesis examples on pages 67 to 134, including both generic and specific chemical pathways. General synthesis schemes for starting materials are included in the specification on pages 67 to 72. Other intermediate compounds and building blocks are discussed on pages 73 to 76, including a further generic parallel synthesis pathway disclosed on pages 84 to 85. These starting materials, intermediates and chemical pathways provide clear guidance to one skilled in the art, such that the skilled practitioner can make and use the full scope of the invention as claimed, by simply making the required substitutions for the X, Y, A, Z and R groups as described in the claims and specification. These starting and intermediate compounds are then used in the disclosed synthetic methods to produce the numerous compounds in the examples which follow on pages 76 to 134.

Further, one skilled in the art could easily follow the General Procedure A on pages 69 to 70, and produce compounds wherein R^3, R^4, R^5, R^6, and A are other than groups described by the Examiner. The general scheme discloses reaction conditions, reagents and solvents, and process steps, including alternative purification methods, which could easily be adapted by one skilled in the

art without undue experimentation to make a variety of compounds covering the full scope of the claimed invention based on the guidance provided in the specification and the practitioner's knowledge of the chemical arts.

The specification also includes guidance as to how one skilled in the art would test the compounds made by following the instructions provided in the specification. On pages 135 to 137 of the specification, guidance is provided as to how one skilled in the art would test the ability of the compounds produced to interact with the H3 receptor. Detailed instructions as to alternative binding assays for testing these compounds are provided. The binding assay procedures described in the specification include the materials required for performing the assays (source materials, buffers, reagents, filters, etc.), testing steps and conditions, suggested equipment, and a discussion of the analysis of the test results.

Thus, the full scope of the pending claims are supported by the specification, in combination with the knowledge of one skilled in the art, such that sufficient guidance and direction are provided and no undue experimentation is needed to practice the full scope of the invention as claimed. Furthermore, it is respectfully submitted that the teaching in the application, in combination with the knowledge of one skilled in the art, fully enables one skilled in the art to make and use the full scope of the claimed invention without undue experimentation

2. The scope of a functional group which can be converted to hydrogen *in vivo* is allegedly not adequately enabled by the specification

Applicants respectfully traverse the rejection. However, in order to advance prosecution, claim 1 has been cancel. New claim 68 recites various functional groups that can be converted to hydrogen i*n vivo*. These functional groups are specifically recited in the specification. Therefore, this ground for rejection has been overcome.

3. In claims 46 and 48, the instant claim language embraces disorders not only for treatment but also for prevention

Applicants respectfully traverse the rejection. However, in order to advance prosecution, claims 46 and 48 have been canceled. New claims 97-98 recite that the method is directed to

methods of treatment. Applicants do reserve the right to file subsequent continuation and/or divisional applications on canceled subject matter.

For the foregoing reasons, Applicants submit that the claims overcome this rejection under the first paragraph of 35 U.S.C. § 112. Applicants respectfully request reconsideration and withdrawal of the rejection.

B. Written Description

Claims 1-3, 5-44, 46, and 48 were rejected under 35 U.S.C. § 112, first paragraph as lacking support for negative limitations. *Ex parte Graselli*, 231 USPQ393 (Bd. App. 1983) aff'd mem., 738 F.2d 453 (Fed. Cir. 1984).

Applicants respectfully traverse the rejection. *Contra* to the Examiner's position, there is sufficient support for the provisos stated in claim 68. Although, *Graselli* does hold that any negative limitation or exclusionary proviso must have basis in the original disclosure, Applicants note that the MPEP §2173.05(i) states that

> If alternative elements are positively recited in the specification, they may be explicitly excluded in the claims. See I*n re Johnson*, 558 F.2d 1008, 1019, 194 USPQ 187, 196 (CCPA 1977) ("[the] specification, having described the whole, necessarily described the part remaining.").....Note that a lack of literal basis in the specification for a negative limitation may not be sufficient to establish a *prima facie* case for lack of descriptive support. *Ex parte Parks, 30 USPQ2d 1234*, 1236 (Bd. Pat. App. & Inter. 1993.

Copies of both of these cases are attached hereto as Exhibits 1 and 2. In *Johnson*, the claim was amended to recite the provisos

> That E and E' may not both include a divalent sulfone group and may not both include a divalent carbonyl group linking two aromatic nuclei.

Even though the specification in *Johnson* contained the statement "Any electron withdrawing group can be employed as the activator group in these compounds", the court held that the disclosure was sufficient to support the two provisos. In the court's view, the specification also discusses preferred embodiments, alternative embodiments, and the practical limits of operation. The court specifically held

> While the board found that "no antecedent basis exists in the parent case" for the "limited genus" in claim 1, we see more than ample basis for claims of such scope. The 1963 disclosure is clearly directed to polymers of the type claimed. Fifty specific choices are mentioned for the E precursor compound, a broad *class* is

> identified as embracing suitable *choices* for the E' precursor compound and twenty-six "examples" are disclosed which detail fifteen species of polyarylene polyethers. Only fourteen of those species and twenty-three of the "examples" are within the scope of the claims now on appeal. Two of the many choices for E' and E' precursor compounds are deleted from the protection sought, because appellant is *claiming less* than the full scope of his disclosure.

Similarly, in the instant application, many embodiments and preferred embodiments are disclosed and there are relatively few exclusions.

Applicants note that *Parks* was actually decided after *Graselli*. The *Graselli* decision was referred to and distinguished in *Park*.

For the foregoing reasons, Applicants submit that the new claims overcome the rejections under 35 U.S.C. § 112, first paragraph, written description. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection.

III. The Rejection of Claims 1-3, 5, 7-11, 20, 33-44, 46, and 48 under 35 U.S.C. § 102

Claims 1-3, 5, 7-11, 20, 33-44, 46, and 48 are rejected under 35 U.S.C. § 102 for allegedly being anticipated by the following references: Arcari et al., DE 2700012; Hauck et al., Chem Abstract 92:146611; Yutilov et al., Chem Abstract 99:70725; Vincent et al., Chem Abstract 117:251781. Applicants will address each of these prior art rejections separately.

A. Arcari et al.

Claims 1,2, 7-13, 15, 20-23, 25, 30, 32 and 33-37 remain rejected under 35 U.S.C. 102(b) as being anticipated by Arcari et al. It is asserted that in the instant claims, X can be C(O), Y can be NH and Z can be alkyl.

Applicants respectfully traverse the rejection. Specifically, Applicants note that one of the provisos in new claim 68 recites

> when X is -CO-, the group -Y-A-Z starts with the radical -NH-, R^1= hydrogen, the remainder of the group -Y-A-Z must not be unsubstituted or C_{1-6}-alkoxy substituted phenyl, unsubstituted C_{3-8}-cycloalkyl or unsubstituted C_{1-6}-alkyl

with drawn

This proviso would specifically exclude material disclosed in Arcari. Acari recites in lines 19-24

> R3 is a hydrogen atom, an alkyl or alkenyl group having from 1 to 6 carbon atoms or a cycloalkyl group having from 3 to 6 carbon atoms or an aromatic group

Therefore, the new claimsJ are not anticipated by Arcari and Applicants respectfully request that the rejection be withdrawn.

B. Hauck et al.

Claims 1, 2, 7-14, 18, 20-23 and 33-37 remain rejected under 35 U.S.C. 102(b) as being anticipated by Hauck et al. It is asserted that A can be an alkylene group while X and Y can be a bond.

Applicants respectfully traverse the rejection. Specifically, Applicants note that the hydroxy group of $-CH_2CH(OH)CH_2$ disclosed in Hauck is not included in new claims 68-101. Therefore, new claims 68-101 are not anticipated by Hauck et al. and Applicants respectfully request that the rejections be withdrawn.

C. Yutilov et al.

Claims 1, 2, 7-14, 18, 20-23 and 33-37 remain rejected under 35 U.S.C. 102(b) as being anticipated by Yutilov et al. It is asserted that A can be an alkylene group while X and Y can be a bond.

Applicants respectfully traverse the rejection. Specifically, Applicants note that the hydroxy group of $-CH_2CH(OH)-$, which is not included in the pending claims or in the new claims presented. Therefore, the new claims are not anticipated by Yutilov et al. and Applicants respectfully request that the rejections be withdrawn.

D. Vincent et al.

Claims 1-3, 5-13, 20-23 and 33-37 remain rejected under 35 U.S.C. 102(b) as being anticipated by Vincent al. It is asserted that the instantly claimed compounds read on the reference compound.

Applicants respectfully traverse the rejection. In the compound of formula I of the instant application, a COOH side chain in new claim 68 not encompassed in the position of R^5 or R^6 which are both hydrogen. Therefore, the new claims are not anticipated by Vincent et al. and Applicants respectfully request that the rejections be withdrawn.

VII. Rejection of the Claims Under 35 U.S.C. § 103

The claims have been rejected under 35 U.S.C. §103 as being unpatentable over (a) Arcari et al., (b) Scarponi et al. and (c) Kureha et al. Each rejection will be addressed separately below.

A. Arcari et al.

The claims have been rejected under 35 U.S.C. 103(a) as being unpatentable over Arcari et al. for the same reasons given in the above 102 rejection. Applicants traverse the rejection for the same reason as for the above 102 rejection. Specifically, one of the provisos in new claim 68specifically disclaimed the disclosure of Arcari et al. Clearly, new claim 68 would not be obvious in view of Arcari et al. Therefore, Applicants respectfully request that the rejection under 35 U.S.C. 103 be withdrawn.

B. Scarponi et al.

Claims 1-3, 5, 7-13, 15, 20-23, 25 and 33-37 remain rejected under 35 U.S.C. § 103 as being unpatentable in view of Scarponi et al., GB 2158440. It is asserted that although Applicants' arguments have included a proviso to overcome the 102 rejection of the same reference, the proviso does not exclude all the possible compounds that can be made following the generic teachings in the reference. It is noted that R1 and R2 of the reference compounds can be a benzyl group that is not covered by the proviso. It is concluded that one of ordinary skill in the art would have been motivated to select the claimed compounds from the genus in the reference since such compounds would have been suggested by the reference as a whole.

Applicants respectfully traverse the rejection. A finding of obviousness under 35 U.S.C. §103 requires a determination of the scope and content of the prior art, the differences between the claimed invention and prior art, the level of ordinary skill in the art, and whether the differences are such that the claimed subject matter as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made. *Graham v. Deere*, 383 U.S. 1 (1966). The structure of formula I recited in new claim 68 is significantly different from the formula I of Scarponi et al. Specifically, the carbon of instant formula I equivalent to carbon #6 of Scarponi does not contain any side chain. In contrast, the carbon #6 contains the side chain $-CON(R_7)R_6$. Therefore, given the structural differences between the two compounds, one of ordinary skill in the art would not have a reasonable expectation of success that given that the

4,5,6,7-tetrahydroimidazo [4,5-c]pyrimidine derivatives have antiviral activity that the compounds encompassed by formula I would or could have a pharmacological effect.

Accordingly, the Scarponi reference fails to provide the necessary incentive or motivation for modifying the reference in a manner that would produce the invention as claimed. For the foregoing reasons, Applicants submit that the amended claims overcome this rejection under 35 U.S.C. § 103 and respectfully request reconsideration and withdrawal of the rejection.

C. The Rejections Over Kureha et al.

Claims 1-3, 5-15, 20-23, 29-37 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Kureha et al. It is asserted that although Applicants' arguments have included a proviso to overcome the 102 rejection of the same reference, the proviso does not exclude all the possible compounds that can be made following the generic teachings in the reference. It is noted that R1 may not only be hydrogen. It is concluded that one of ordinary skill in the art would have been motivated to select the claimed compounds from the genus in the reference since such compounds would have been suggested by the reference as a whole.

Applicants respectfully traverse the rejection. The compounds encompassed by formula I of new claim 68 and formula I of Kureha et al. are significantly different from one another. Specifically, in Kureha, R2 is carbamoyl, mono- or di-C1-C6 alkylcarbamoyl, 4-5 membered heterocyclic carbamoyl. In formula I of the instant invention, R2 would be hydrogen only. Given the structural differences between the two compounds, one of ordinary skill in the art would not have a reasonable expectation of success that given that the 4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine-6-carboxylic acid amide derivatives are angiotensin II antagonists, that the compounds encompassed by formula I would or could have a pharmacological effect. Specifically, Kureha provides no teaching or suggestion that the disclosed compounds would have any histamine H3 receptor activity. Furthermore, there is no suggestion or motivation in Kureha that the disclosed compounds or any modifications thereof would possess any activity related to the histamine H3 receptor of the claimed compounds and be active in the treatment of disease associated with the histamine H3 receptor.

Accordingly, the Kureha reference fails to provide the necessary incentive or motivation for modifying the reference in a manner that would produce the invention as claimed. For the foregoing reasons, Applicants submit that the amended claims overcome this rejection under 35

U.S.C. § 103 and respectfully request reconsideration and withdrawal of the rejection.

VI. Conclusion

In view of the above, it is respectfully submitted that all claims are in condition for allowance. Early action to that end is respectfully requested. The Examiner is hereby invited to contact the undersigned by telephone if there are any questions concerning this amendment or application.

Respectfully submitted,

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